

CASE REPORT

## Key clinical features a general internist needs to know about Brugada syndrome: a case-based discussion

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**Introduction:** Brugada syndrome (BrS) is an autosomal dominant genetic disorder involving the abnormal function of cardiac voltage-gated sodium ion channels. Sodium channel loss of function can lead to early repolarization and loss of the Phase 2 action potential dome in cardiomyocytes. In BrS, this sodium channelopathy occurs in some, but not all, epicardial cells thus creating 1) juxtaposition of depolarized and repolarized cells in the epicardium and 2) a transmural voltage gradient. Together, these conditions can set up a Phase 2 reentry and resultant malignant cardiac arrhythmia. Of the three types of electrocardiogram (EKG) changes seen in BrS, only the Type 1 EKG is considered diagnostic. In a controlled setting, sodium channel blockers and Brugada EKG leads may be used to unmask this diagnostic EKG finding. Fever and certain medications that interfere with the sodium channel can also trigger these changes, which can be catastrophic.

**Case report:** A 26-year-old white male presented with febrile upper respiratory infection symptoms and had an EKG change, which was initially misinterpreted as an ST elevated myocardial infarction due to ST-T segment elevation in leads V1 and V2. The patient reported past recurrent syncopal episodes leading to a recent suspected diagnosis of BrS. A later episode of febrile illness, triggering a Type 1 EKG pattern, led to a subsequent hospital admission for continuous cardiac monitoring. On that occasion, he was placed on a wearable external defibrillator pending placement of implantable cardioverter defibrillator (ICD) device.

**Conclusion:** Due to the gravity of symptoms that can manifest in the BrS patient, it is important to recognize and treat this condition promptly and effectively. BrS patients require admission for continuous cardiac monitoring when febrile and certain medications interfering with the sodium channel should be avoided in this population. Although medications may be used as one treatment modality, definitive therapy is placement of an ICD device.

Keywords: *Brugada syndrome; sodium channelopathy; sudden cardiac arrest; implantable cardioverter defibrillator*

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First identified in 1992 (1), Brugada syndrome (BrS) is a rare cause of sudden cardiac arrest (SCA) in otherwise healthy young patients. BrS is an autosomal dominant genetic disorder associated with genetic defects such as a 'loss-of-function' mutation in the *SCN5A* gene resulting in abnormal function of myocardial sodium channel activity (2). Overall prevalence of BrS is estimated to be 5/10,000 with a higher prevalence seen in Southeast Asia. Men have a higher prevalence with a male to female ratio of 8–10:1. BrS accounts for 4–12% of all sudden cardiac death (SCD) and up to 20% of SCDs in the absence of structural heart disease (3).

Most patients have symptoms which manifest in their 30s. Presentation can include palpitations, syncope, seizures, nocturnal agonal respiration, and atrial fibrillation.

The most serious clinical symptoms of BrS include SCA secondary to ventricular tachycardia (VT) or ventricular fibrillation (VF). Characteristic signs seen on electrocardiogram (EKG) include pseudo-right bundle branch block and persistent ST-segment elevation in leads V1–V3 (4). Although medications may be used to treat this syndrome, implantable cardiac defibrillator (ICD) is the only definitive therapy (5).

### Case presentation

A 26-year-old male initially presented to the emergency department with cough, sore throat, and fever. An ST elevated myocardial infarction alert was called based on an EKG (Fig. 1), which was ordered for complaint of palpitations. It was later determined by a cardiologist that

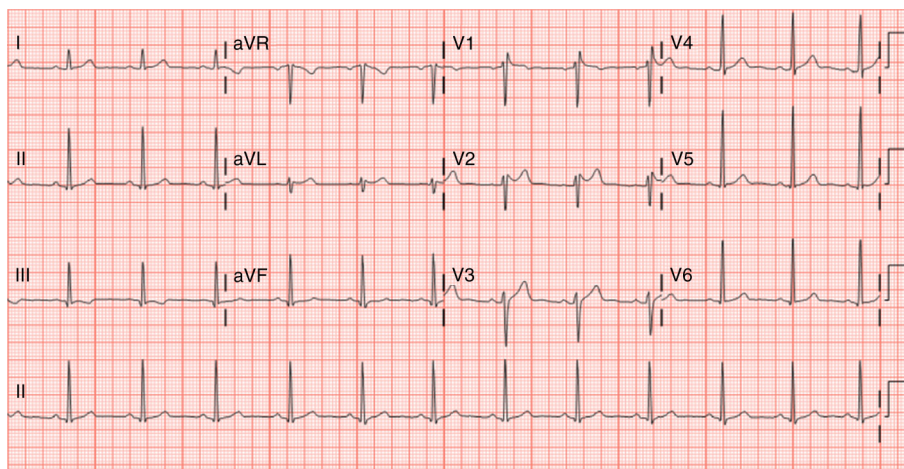


Fig. 1. EKG at the initial encounter (Type 2 BrS EKG).

his EKG, though not diagnostic, was consistent with BrS. Due to his symptoms, the patient was advised to have an ICD or loop recorder placed; however, the patient failed to follow up claiming lack of medical insurance and time commitments at work.

In the following 6 months, he had three syncopal episodes; two at rest and one on exertion while at his workplace where he mixes cement. During his latest syncopal episode, he presented with complaints of nausea, dizziness, and loss of consciousness, all preceded by symptoms consistent with upper respiratory infection (URI) to include cough, sore throat, and fever.

The patient's past medical history was otherwise non-contributory. Family history, while vague, was significant for the early death of his father at 32 years of age from a heart complication and multiple uncles with a history of 'heart disease'. The patient admitted to smoking less than one pack per day for over 15 years, but denied use of alcohol or illicit substances. Physical examination was normal with the exception of a temperature of

102°F and bilateral, scattered, expiratory wheezes on pulmonary exam.

EKG at this time was suggestive of Type 1 Brugada pattern (Fig. 2). Nuclear exercise stress test showed no reversible perfusion defect. 2D echocardiography showed left ventricular (LV) cavity of normal size and function with ejection fraction of 55–60%. Remaining lab data were unremarkable with normal hemoglobin, thyroid stimulating hormone (TSH), and liver/kidney function panels.

Prior to discharge, the patient was fit and instructed on management of a wearable external cardiac defibrillator, which he wore for 2 weeks while awaiting resolution of his URI symptoms. An ICD was later placed and the genetic study of *SNC5A* returned normal.

## Discussion

### Proposed mechanism

Transient outward potassium current ( $I_{to}$ ) is the major channel for repolarization of myocardium during

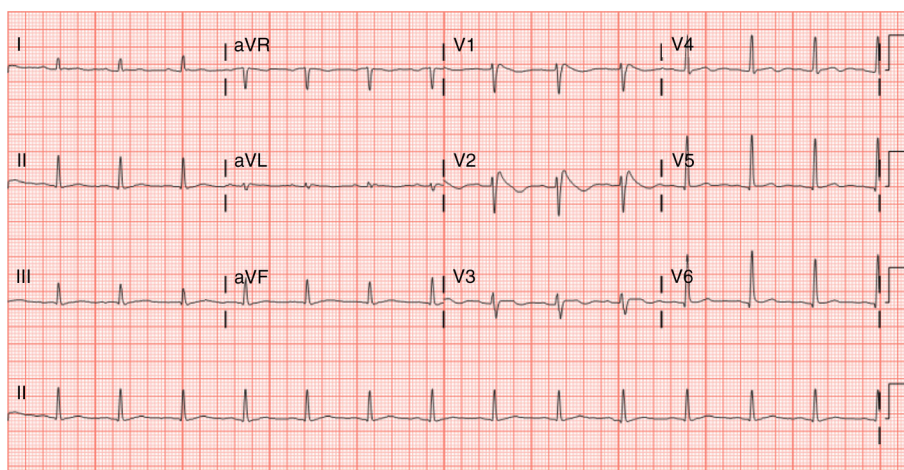


Fig. 2. EKG at the current encounter (Type 1 BrS EKG).

action potential (AP). The normal heart has a higher density of  $I_{to}$  in the epicardium compared to endocardium. Although normally this is biologically insignificant, in patients with a problem of inward currents (e.g., *SCN5A* mutation with sodium channel loss of function) this aberrancy can lead to early repolarization/loss of the Phase 2 AP dome in a percentage of epicardial cells. This creates a juxtaposition of depolarized and repolarized cells in the epicardium leading to epicardial dispersion of repolarization (EDR). It also gives rise to a transmural voltage gradient leading to transmural dispersion repolarization (TDR) between the epicardium and endocardium. EDR and TDR set up the potential for a Phase 2 reentry. Once vulnerable, the AP can propagate from sites of normal repolarization to sites of early repolarization leading to closely grouped premature ventricular complex (PVCs), VT, or VF.

Although *SCN5A* is the most common site of mutation detected in BrS (seen in 18–30% of BrS) (2), other gene mutations that exacerbate the EDR are also reported. These include loss-of-function mutation of *GPD1-L* gene (which also reduces inward sodium current) (6), and gain of function of *KCNE3* or *KCND3* genes (both of which enhance the outward  $I_{to}$ ) (7, 8).

Although once was thought to be a pure channelopathy in the structurally normal heart, recent evidence suggests that BrS may have involvement of mild structural abnormalities (9) such as focal fibrosis, fibrofatty replacement of right ventricular (RV) free wall, and right ventricular outflow tract (RVOT) enlargement. Additionally, conduction delay in the RVOT serves as an alternate mechanism for BrS (10, 11).

### Diagnosis

Diagnosis of BrS requires both clinical findings and characteristic EKG patterns (2). Three types of BrS EKG patterns have been described (4). Type 1 is characterized by a coved-shape ST-segment elevation greater than 2 mm followed by an inverted T wave in one or more of the right precordial leads (V1, V2, and V3). This type of EKG pattern is itself diagnostic of BrS (Fig. 3a). Type 2 EKG pattern is characterized by the ST-segment resembling a saddleback with an ST-segment elevation of at

least 2 mm, a trough of the ST-segment of at least 1 mm and either a positive or biphasic T wave (Fig. 3b). Type 3 pattern consists of either a coved or saddleback ST-segment elevation between 1 and 2 mm (Fig. 3c).

Unlike the Type 1 EKG pattern, Type 2 and 3 alone are not considered diagnostic (Table 1). Additionally, while Type 1 can occur either spontaneously or induced by sodium-channel blockers, Type 2 and 3 must occur spontaneously in order to qualify as a diagnostic factor. Conversion of either Type 2 or 3 to Type 1 EKG pattern is, however, diagnostic for BrS.

It is crucial to emphasize the tendencies for EKG pattern variance in BrS patients over time. As demonstrated in our case presentation, the EKG was Type 2 (Fig. 1) on initial presentation, but Type 1 on the next encounter (Fig. 2). EKGs may present as one of the three aforementioned varieties or appear normal, thus it is important to recognize the various strategies for unmasking BrS in non-diagnostic EKGs.

Because they exacerbate the fundamental pathophysiology of BrS, sodium channel blockers such as procainamide, flecainide, or ajmaline are used in attempt to reveal a Type 1 EKG pattern in the suspected BrS patient. This sodium channel blocker challenge test should be carried out in a highly monitored area equipped to perform cardiac resuscitation, ideally in an electrophysiology (EP) laboratory.

Mild structural abnormalities of the RVOT serve as another fundamental pathophysiology for BrS. Because these abnormalities can distort the EKG findings, the repositioning of leads, called Brugada leads for its namesake, toward the RVOT can increase the detection of characteristic BrS EKG changes (12). In a conventional 12-lead EKG, for instance, leads V1 and V2 are placed to the right and left of the sternum, respectively, at the level of the fourth intercostal space (ICS). Yet when these leads are moved just one or two ICSs cephalad (e.g., to the second or third ICS), it can help unmask BrS on EKG by accommodating for the RVOT abnormalities. This small change can be particularly telling for diagnostic purposes,

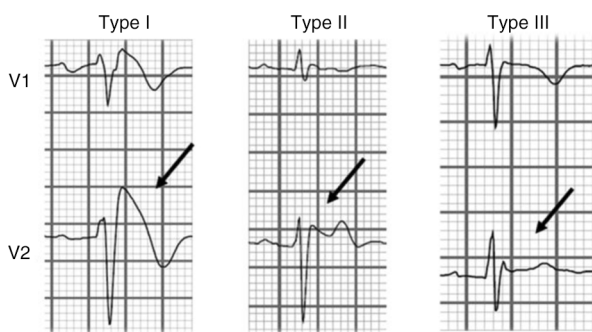


Fig. 3. Three types of EKG of BrS.

Table 1. Diagnosis criteria of three types of BrS EKG

ST-segment abnormalities in the different types of Brugada syndrome			
	Type I	Type II	Type III
J wave amplitude	≥ 2 mm	≥ 2 mm	≥ 2 mm
T wave	Negative	Positive or biphasic	Any
ST-T configuration	Coved type	Saddle back	Either
ST-segment (terminal portion)	Gradually descending	Elevated ≥ 1 mm	Elevated < 1 mm



especially when used in combination with intravenous procainamide administration.

### Differential diagnosis

Below is a list of conditions that may induce ST-segment elevation in the right precordial leads, mimicking BrS EKG. They comprise the differential diagnoses of BrS and should be ruled out before a BrS diagnosis is made: 1) atypical RBBB; 2) early repolarization; 3) left ventricular hypertrophy; 4) acute myocardial infarction (MI, especially RV MI); 5) acute pericarditis/myopericarditis; 6) hemopericardium; 7) dissecting aortic aneurysm; 8) pulmonary embolism; 9) arrhythmogenic RV cardiomyopathy; 10) disorders of central nervous system/autonomic nervous system; 11) Duchenne muscular dystrophy; 12) Friedreich ataxia; 13) mechanical compression RVOT; 14) electrical cardioversion; and 15) hypothermia.

Of note, recent reports have shown that Brugada EKG pattern can also be induced by cocaine toxicity (13, 14).

### Fever and BrS

It is important to be aware of the relationship between fever and BrS. Fever can accentuate inactivation of the  $\text{Na}^+$  channel, which may induce a Type 1 BrS EKG pattern and trigger ventricular arrhythmia, syncope, and even SCA (15–17). This is well demonstrated in our case review of the febrile patient. Any known BrS patient who develops febrile disease should thus be hospitalized for continuous cardiac monitoring if ICD has not yet been implanted.

### Medications to avoid in BrS patient

Any medications that can interfere with sodium channel activity will potentially induce typical EKG change and precipitate cardiac dysrhythmia in the BrS patient. Table 2 lists a brief compilation of common medications that can induce Brugada-like EKG patterns and should ultimately be avoided in all BrS patients.

### Treatment

ICDs are the only established form of effective treatment and should be offered to all symptomatic BrS patients. For asymptomatic patients, more risk stratification studies should be done prior to ICD is implanted. Factors such as family history for SCD, whether EKG pattern is spontaneous versus drug-induced and EP study results should be included in this analysis (2).

Pharmacologic treatment of choice for BrS is quinidine, a class IA antiarrhythmic. Quinidine blocks the  $\text{I}_{\text{to}}$  channel, which, as previously mentioned, plays a predominant role in arrhythmogenesis of BrS. Quinidine can thus normalize ST-segment elevation (18) and decrease both inducible and spontaneous VF (19). It can be used as adjunct therapy with ICD or as the sole therapy, though second-line (20). Alternate pharmacologic therapy includes use of isoproterenol, which, by increasing the  $\text{I}_{\text{CaL}}$

**Table 2.** Medications that may trigger typical EKG changes in BrS patients

I. Antiarrhythmic drugs
1. $\text{Na}^+$ channel blockers
Class IC drugs (flecainide, pilsicainide, propafenone)
Class IA drugs (ajmaline, procainamide, disopyramide, cibenzoline)
2. $\text{Ca}^{2+}$ channel blockers (verapamil)
3. $\beta$ -Blockers (propranolol, etc.)
II. Antianginal drugs
1. $\text{Ca}^{2+}$ channel blockers (nifedipine, diltiazem)
2. Nitrate (isosorbide dinitrate, nitroglycerine)
3. $\text{K}^+$ channel openers (nicorandil)
III. Psychotropic drugs
1. Tricyclic antidepressants
Amitriptyline, nortriptyline, desipramine, clomipramine
2. Tetracyclic antidepressants
Maprotiline
3. Phenothiazine
Perphenazine, cyamemazine
4. Selective serotonin reuptake inhibitors
Fluoxetine
IV. Other drugs
1. Dimenhydrinate
2. Cocaine intoxication
3. Alcohol intoxication

current, has proved to be useful for treating electrical storm in BrS (21).

### Conclusion

BrS is a rare autosomal dominant genetic disorder that can cause SCA secondary to VF or VT. Southeast Asian men are more often affected. Sodium channelopathy and mild structural abnormalities of RV outflow tract are believed to be part of its underlying pathophysiology. There are three characteristic EKG patterns, but only Type 1 is diagnostic. This type can be induced by sodium channel blockers and/or Brugada EKG leads. Because fever can trigger Type 1 EKG changes precipitating dysrhythmia, febrile BrS patient should be hospitalized for continuous cardiac monitoring until a form of defibrillator is implemented. In addition, certain medications should be avoided in BrS patients. For symptomatic patients, wearable external defibrillator devices should be used until a more definitive treatment modality is established. Pharmacologic therapy is less effective, but may serve as an adjunct in treatment. ICD is the only proven effective treatment modality.

### Conflict of interest and funding

The authors declare no conflicts of interest.

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